CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-505

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	September 3, 2010
To:	Mary Parks, M.D., Director Division of Metabolism and Endocrinology Products (DMEP)
Thru:	Claudia Karwoski, Pharm.D., Director Division of Risk Management (DRISK)
From:	**Egrifta DRISK Review Team** Marcia Britt, Ph.D., Health Education Reviewer Cynthia LaCivita, Pharm.D., Risk Management Analyst Gita Toyserkani, Pharm.D., M.B.A., Acting Team Leader Jodi Duckhorn, M.A., Assessment Team Leader Latonia Ford M.S., B.S.N., R.N., Patient Product Information Reviewer
Subject:	Review of Risk Evaluation and Mitigation Strategy (REMS) for Egrifta
Drug Name(s):	Egrifta (tesamorelin acetate for injection)
Submission Number: Application Type/Number:	NDA 22-505
Applicant/sponsor:	Theratechnologies, Inc. & EMD Serono, Inc.
OSE RCM #:	2009-1555

INTRODUCTION

This review follows a request from the Division of Metabolism and Endocrinology Products (DMEP) for the Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRISK) to evaluate the proposed Risk Evaluation and Mitigation Strategy (REMS) for Egrifta (tesamorelin acetate for injection).

2 BACKGROUND

On May 29, 2009, Theratechnologies, Inc./EMD Serono Inc. submitted a new drug application (NDA 22-505) for Egrifta (tesamorelin acetate for injection). Egrifta is a growth hormone releasing factor (GHRF) that acts on pituitary somatotroph cells to trigger growth hormone (GH) synthesis and secretion, in part by raising circulating levels of insulin-like growth factor-1 (IGF-1). The proposed indication is to induce and maintain a reduction of excess abdominal fat in human immunodeficancy virus (HIV)-infected patients with lipodystrophy.

HIV-lipodystrophy syndrome is characterized by increased visceral adipose tissue and a wasting of subcutaneous fat in the limbs. Lipodystrophy has a negative impact on a patient's self image, and increases in visceral adipose tissue (VAT) are associated with metabolic disturbances which in turn are risk factors for type-2 diabetes and cardiovascular disease. The premise for this drug development is that in addition to improving patient's self image, a decrease VAT and an improvement in the distribution of VAT relative to subcutaneous adult tissue (SAT) could be associated with improvement in metabolic disorders and decrease cardiovascular risk.

The recommended dose of EGRIFTA is 2 mg in 2 mL, injected subcutaneously once a day, preferably in the abdomen. The 2 mg dose requires reconstitution of 2 vials of drug product using 2.2 mL Sterile Water for Injection from a single use 10 mL vial. The patient is instructed to combine the contents for a single injection.

At the pre-NDA meeting held on September 19, 2008, the sponsor asked whether the Agency agreed that REMS for Egrifta was not necessary. The sponsor was informed that a decision regarding the need for a REMS would be made after the NDA submission had been thoroughly reviewed.

During a teleconference on September 30, 2009, DMEP expressed concern about unfavorable immunologic risk-benefit if Egrifta were prescribed inappropriately to large numbers of obese HIV- patients who may be more severely immunocompromised. The Agency encouraged the sponsor to submit a REMS which would diminish the likelihood of inappropriate use of Egrifta.

The proposed REMS and REMS supporting document were submitted on December 14, 2009. A revised REMS supporting document, that included additional safety and risk information, was submitted on May 12, 2010. In the proposed REMS for Egrifta, the sponsor identified hypersensitivity reactions, glucose homeostasis, and increased IGF-1 levels as the key safety concerns. The proposed REMS consists of a Medication Guide, Communication Plan (Dear Healthcare Provider Letter and Dear Pharmacists Letter), and

Timetable for Assessment (12 months, 2 years, 3 years, 5 years and 7 years from approval).

The Endocrinologic and Metabolic Drugs Advisory Committee for Egrifta was held on May 27, 2010. Sixteen members of the advisory committee (AC) voted yes, in favor of drug approval; with zero no's or abstentions. Although, the AC was in favor of drug approval, the general consensus was that post marketing studies or a registry was needed to answer questions about Egrifta with regard to cardiovascular benefit and risk; glucose control; elevated IGF-1 levels and malignancy; and to determine if patients who are non-responders can be identified.

3 MATERIALS REVIEWED

The following document(s) were reviewed:

- Theratechnologies, Inc./EMD Serono Inc. proposed REMS submission submitted December 14, 2010
- Theratechnologies, Inc./EMD Serono Inc. proposed REMS supporting document submitted on December 14, 2010
- Theratechnologies, Inc./EMD Serono Inc. proposed Prescribing Information (PI) for Egrifta® (tesamorelin acetate) for injection, October 30, 2009
- Tesamorelin (Egrifta) Advisory Committee Briefing Document submitted April 27, 2010
- Theratechnologies, Inc./EMD Serono Inc. revised REMS supporting document dated May 10, 2010
- Egrifta (tesmoreline acetate) for injection, DMEPA Label and Labeling Review, Miller CA, March 1, 2010
- Valtropin™(somatropin recombinant) approved label dated April 19, 2007
- Nutropin™(somatropin recombinant) approved label dated November 17, 1993
- Genotropin™ (somatropin recombinant) approved August 24, 1995
- Omnitrope™ (somatropin recombinant) approved May 30, 2006

4 ANALYSIS TECHNIQUES

The REMS submission was reviewed for conformance with Title IX, Subtitle A, Section 901 of the Food Drug Administration Amendments Act of 2007 (FDAAA). In addition, the Egrifta REMS was considered and compared to risk mitigation strategies used for other approved growth hormones and growth hormone releasing-hormones.

5 REVIEW OF THE SAFETY PROFILE

5.1 Pivotal Trials

TH9507//III/LIPO/010, TH9507-CTR-1011, and TH9507-CTR-1012 were the three, phase 3 trials used to support the application and were evaluated for safety signals that might indicate the need for a REMS. Summaries of the three trials are provided below.

TH9507//III/LIPO/010 was a randomized, multi-centered, double-blind, placebo-controlled trial that evaluated the efficacy and safety of a 2 mg daily dose of Egrifta in

patients with HIV-lipodystrophy. There were two phases in this trial, the main phase and the extension phase. The main phase was 6 months in duration and randomized patients to drug or placebo at a 2:1 ratio. At the end of the main phase patients who finished treatment with Egrifta were re-randomized 3:1 to either Egrifta or placebo. In addition, patients who received placebo in the main phase were directly switched to 2 mg of Egrifta daily during the extension phase. The primary end-point was a change from baseline in visceral adipose tissue defined as cross-sectional area in cm^2 measured by CT scan at the L4-L5.

TH9507-CTR-1011 was also a randomized, double-blind, placebo-controlled, multicenter trial, that evaluated the efficacy and safety of a 2 mg daily dose of Egrifta in patients with HIV-lipodystrophy. The trial was 6 months in duration and randomized patients to drug or placebo at a 2:1 ratio.

TH9507-CTR-1012 was a 6-month extension of TH9507-CTR-1011 trial and similar in design to the extension phase of TH9507/III/LIPO/010, with the exception that patients who completed Egrifta were equally randomized to either drug or placebo. All patients who initially completed the placebo arm were then switched to Egrifta 2 mg daily.
The same inclusion criteria and assessments of efficacy and safety were used for all three studies. To be included in the trials patients needed to meet the following criteria:18-65 years, HIV positive with a CD4 count >100 cells/mm^3, viral load <10,000 copies/mL, stable on retroviral regimen for 8 weeks prior to randomization, clinical manifestations of HIV lipodystropy, and evidence of abdominal fat accumulation (i.e., males, waist circumference $\geq$ 95 cm and a hip-to-waist ratio $\geq$ 0.94; females waist circumference $\geq$ 94 cm and a hip-to-waist ratio $\geq$ 0.88).

Patients were excluded from the trials if they had: malnutrition (BMI $\leq$ 20 kg/m2), recent opportunistic infections, type 1 diabetes, type 2 diabetes if previously treated with insulin or with oral hypoglycemic or sensitizing agents, fasting blood glucose $\geq$ 150 mg/dL, history of malignancy, hypopituitarism, change in anti-hyperlipidemic treatment within 3 months, receiving estrogen therapy, or had changes in testosterone regimen and/or use of supraphysiological doses of testosterone or anabolic steroid within 6 months.

The sum of the three trials included a total of 816 patients that were randomized to Egrifta (N=550) and placebo (N=266).

In trials TH9507//III/LIPO/010 and TH9507-CTR-1011 a daily subcutaneous injection of 2 mg of Egrifta when compared to placebo at 26 weeks was statistically superior at demonstrating a decrease in visceral adult fat (VAT) defined as cross-sectional area in cm^2 measured by CT scan at the L4-L5. Patients that moved on to the extension arm and were randomized from Egrifta to placebo were not able to maintain a decrease in VAT.

Concerns and observations from these trials regarding safety are addressed in the following section.

5.2 Specific Safety Concerns

5.2.1 *Injections sites reactions* were the most frequently reported adverse events and occurred more frequently in the Egrifta arm when compared to placebo, 34.8% and 24.7%, respectively. In the main phase of both trials adverse events associated with the injection-site were recorded as: erythema; pruritis; peripheral edema; and pain. The adverse effects associated with the administration of Egrifta are similar to adverse events reported for other growth hormones which includes myalgia, arthralgia, joint stiffness and swelling, peripheral edema, paresthesia, hypoesthia, peripheral neuropathy and carpal tunnel syndrome.

5.2.2 *Hypersensitivity reactions* were more prevalent in the Egrifta arm when compared to placebo, 26 patients and 1 patient, respectively. None of the hypersensitivity reactions were reported to anaphylaxis.

5.2.3 *Anti-tesamoreline IgG antibodies* were detected in half of the patients treated with Egrifta. Increases in titers were reversible and antibodies declined in the majority of patients when Egrifta was stopped. The presence of antibodies did not appear to impact VAT response or adverse events with the exception of a reported increase in upper respiratory infections in the extension phase (Egrifta 11.1% and placebo 3.0%).

5.2.4 *Glucose metabolism* Patients included in the trials were permitted to have mildly impaired glucose metabolism (fasting blood glucose of $\leq$ 150 mg/mL), but were excluded if they had type 1 or 2 diabetes and if they were treated with insulin, oral hypoglycemic or sensitizing agents. In both main phases, at week 26 there were no considerable changes in mean values for fasting blood glucose, fasting insulin, homeostatis model assessment-insulin resistance (HOMA-IR) and HbA1c between Egrifta and placebo-treated patients. However, there was a statistically significant difference in the number of patients who developed diabetes mellitus in the Egrifta group when compared to placebo. Post-baseline evaluations noted a trend toward worsening glucose status in individual patients treated with Egrifta but, patients who continued on Egrifta in the extension trials did not have a continued decline in glucose control.

5.2.5 *Cancer* In the pivotal trials a total of 15 patients were diagnosed with cancer; 12 had received Egrifta and 3 were in the placebo group. Treating physicians believed that only one patient in the Egrifta group and one patient in the placebo group were related to treatment; both patients had Hodgkin's.

5.2.6 *IGF-1 response* Baseline IGF-1 levels in both main studies were reported to be less than 2 SD for over 90% of the patients. At 26 weeks the IGF-1 levels in the placebo group remain essentially the same; the percentage of patients that received Egrifta that had IGF-1 above the upper limit of normal increased from 6.2% to 47.4%. Approximately ½ of the patients had IGF-1 levels greater than 2 Standard Deviations (SD) and 1/3 had IGF-1 levels over 3 SD. The difference in IGF-1 levels between Egrifta and placebo were statically significant.

5.2.7 *Hypophysectomy/hypopituitarism* - Egrifta is contraindicated in patients with disruption of the hypothalamic-pituitary axis and therefore these patients were excluded from the pivotal trials.

5.2.8 *Inappropriate Use*- Potential use of Egrifta for muscle enhancement or weight loss.

5.2.9 *Proposed packaging* – The proposed two-box kit that requires reconstitution of 2 separate vials which are combined to produce the 2 mg dose, has a the potential to contribute to medication errors.

6 PROPOSED REMS

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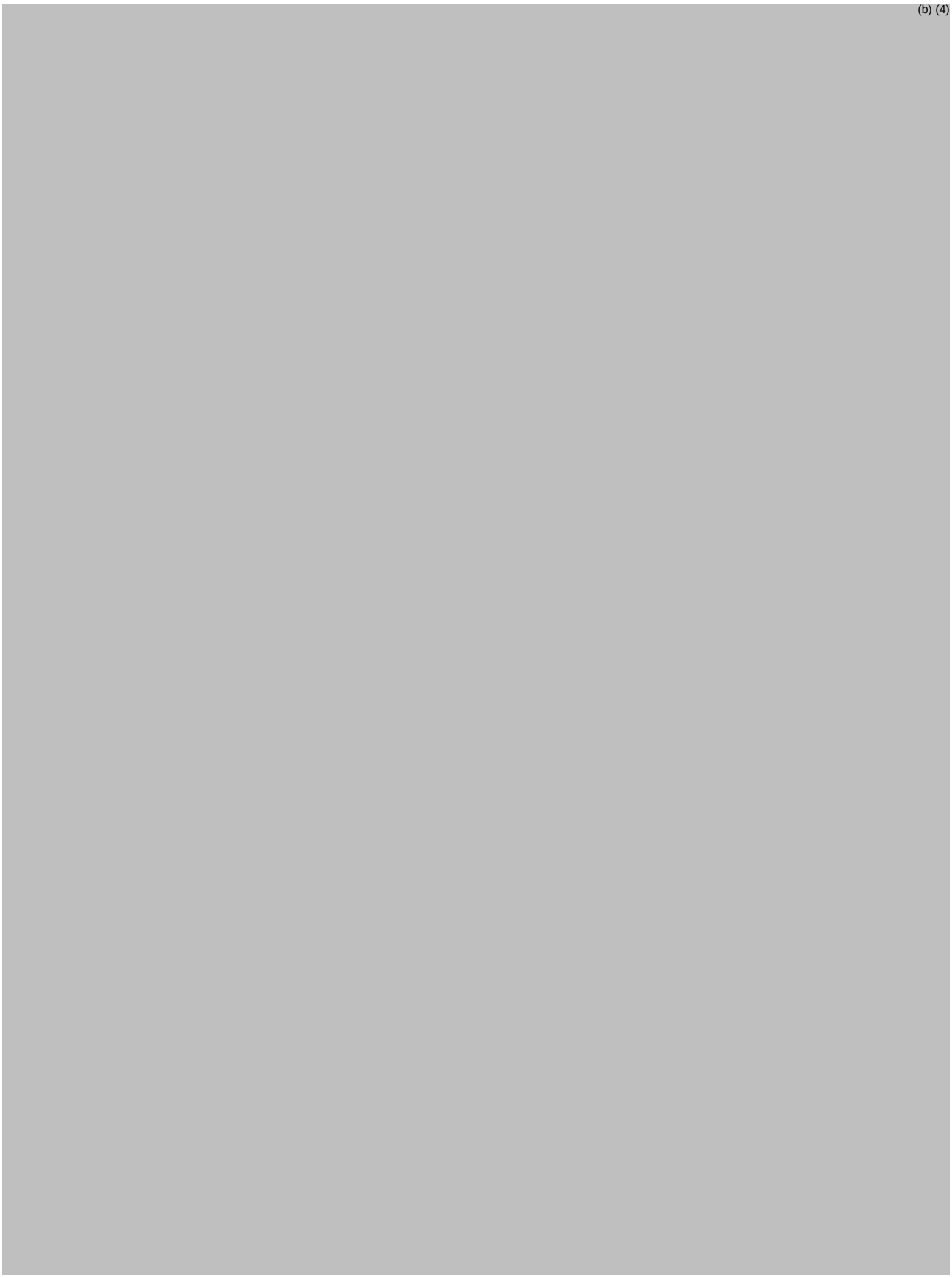
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8 CONCLUSION

After a careful review of the available safety data on Egrifta, and a comparison to approved growth hormones, we believe that the previously mentioned safety issues do not warrant a risk mitigation strategy. There were no new or unique safety concerns associated with Egrifta in the pivotal trails when compared to currently approved growth hormones. At this time, none of the approved human growth hormones have REMS. Post marketing studies are needed to evaluate longer periods of use in a greater number of patients to determine the risk and safety profile with extended-use in patients with HIV. We defer comments on packaging, post marketing studies and surveillance to the Divisions of Medication Error Prevention and Analysis and Epidemiology, respectively and. If new safety issues emerge a REMS could be warranted to ensure that the benefits of therapy outweigh the risks.

DRISK believes that the sponsor should include a patient package insert with attached instructions for use as part of each "kit" of Egrifta. The sponsor submitted a Medication Guide; text from the guide will be used to populate the patient packet insert. Specific comments on the patient package insert and the instructions for use will be addressed in a separate review.

Lastly, while we do not believe that a restricted distribution plan is necessary to ensure the benefits outweigh the risks, we are not opposed to the sponsor employing methods to decrease inappropriate prescribing as they deem necessary.

9 RECOMMENDATIONS

DRISK has the following recommendations and comments for DMEP regarding Egrifta.

1. At this time, a REMS for Egrifta is not needed.
2. The patient package insert and instructions for use need to be included in each Egrifta kit.
3. Revise the dosage so that the complete 2 mg dose is packaged in one vial.
4. The applicant's restricted distribution plan outside of REMS designed to curtail inappropriate use is acceptable.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22505	ORIG-1	THERATECHNOLOGIES INC	Egrifta

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/s/

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